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REVIEW ARTICLE

Clinical and Public Health Considerations for HPV Vaccination in Midadulthood: A Narrative Review

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Human papillomavirus (HPV) is an important cause of anogenital and oropharyngeal cancers, anogenital warts, and recurrent respiratory papillomatosis. Beginning in 2019, US guidelines recommended shared clinical decision-making (SCDM) for HPV vaccination among midadults (27–45 years). We conducted a narrative review of existing literature on HPV vaccination in midadults. The available evidence demonstrates that HPV vaccination in midadults is safe, efficacious, and likely to benefit both HPV-naïve midadults and those with previous infections. However, gaps in knowledge related to HPV vaccination have been identified among clinicians and midadult patients. Universal midadult HPV vaccination in the United States could avert 20 934–37 856 cancer cases over 100 years, costing $141 000–$1 471 000 per quality-adjusted life-year gained. Wide variation in these estimates reflects uncertainties in sexual behavior, HPV natural history, and naturally acquired immunity. Greater awareness among clinicians and midadult patients and broad implementation of SCDM may accelerate progress toward eliminating HPV-associated cancers and other diseases.

Keywords. HPV; human papillomavirus; midadults; vaccination.

Human papillomavirus (HPV) is an important cause of anogenital and oropharyngeal cancers, anogenital warts, and recurrent respiratory papillomatosis (RRP). Over 200 HPV types have been identified, 12 of which have known oncogenic potential, with another 13 potentially oncogenic types [1]. A 9-valent HPV vaccine (9vHPV), effective against the HPV types responsible for approximately 90% of all cases of cervical cancer and anogenital warts (HPV 6/11/16/18/31/33/45/52/58) [2], is recommended by the US Advisory Committee on Immunization Practices (ACIP) for routine use in children aged 11–12 years (and can be given starting at age 9 years), with catch-up vaccination recommended for unvaccinated individuals aged ≤26 years [3]. These age groups are targeted to establish immunity before sexual exposure to HPV.

In 2018, the US Food and Drug Administration expanded approval of 9vHPV to include midadults aged 27–45 years [4]. The ACIP recommends that HPV vaccination in midadults be based on shared clinical decision-making (SCDM) [3]. SCDM is a process by which clinicians and patients work together to make a decision based on risks, benefits, and patient preferences. However, there may be uncertainty in operationalizing SCDM for adult vaccinations in clinical practice [5].

We conducted a narrative review to describe the available evidence and considerations in SCDM for HPV vaccination in midadults. The objectives of this narrative review are to (1) review evidence on the safety and efficacy of HPV vaccination in midadults; (2) describe the clinical rationale for midadult HPV vaccination; (3) summarize evidence on public health impacts of midadult vaccination; (4) review the cost-effectiveness of this approach; (5) describe considerations for SCDM for HPV vaccination; and (6) describe uptake and patient and clinician knowledge of midadult HPV vaccination.

Existing Studies Demonstrate That HPV Vaccination Is Safe and Efficacious in Midadults

Randomized controlled trials (RCTs) have assessed the safety and efficacy of quadrivalent HPV vaccination (4vHPV; recommended for use in the United States since 2006) among midadults, but none have evaluated 9vHPV. Regulatory agencies have concluded that 4vHPV vaccine efficacy results can be bridged to 9vHPV [6]. Efficacy against persistent infections, cervical intraepithelial neoplasia (CIN), and external genital lesions related to HPV 6/11/16/18 was 89% among women in per-protocol analyses after 4 years in the Future III trial, conducted among 3819 women 24–45 years [7]. Efficacy was lower in the older age group (35–45 years: 84%) compared with the younger age group (24–34 years: 91%), but differences were not statistically significant. Durable protection for up to

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10 years was observed in an extension of this study [8]. Results of a phase II trial to establish the immunogenicity and safety of 4vHPV in men ages 27–45 years found that 100% of participants (n = 150) seroconverted to the 4 HPV vaccine components [9]. The immune response in midadult men was comparable to that observed in younger men, in whom clinical efficacy has been demonstrated.

Clinical Rationale for HPV Vaccination Among Midadults

Without vaccination, the lifetime probability of infection with ≥1 HPV type among sexually active individuals with opposite-sex partners was estimated at >84% [10]. Vaccination may benefit midadults at risk of incident infection through new sexual partnerships. Midadults and older age groups continue to form new partnerships [11] and acquire other sexually transmitted infections [12]. Notably, 23%–33% of sexually active men and 15%–25% of sexually active women ages 25–49 years in the United States are infected with ≥1 high-risk HPV type, suggestive of ongoing acquisition in some midadults [13].

Concerns exist that midadult vaccination may have limited benefit for adults already exposed to HPV. However, despite exposure to and infection with ≥1 HPV type over their lifecourse, few midadults have immunity to all HPV types covered by 9vHPV [13]. Thus, vaccination would confer immunity among midadults against types to which they have not yet been exposed. Additionally, even among midadults with prior HPV infection, protective immunity against same-type reinfection is uncertain. Presence of naturally acquired antibodies has been inconsistently associated with protection against type-specific reinfection among women [14, 15]. Studies among men have failed to identify protective effects of naturally acquired antibodies against reinfection [16, 17]. The existing evidence suggests that natural immunity alone provides insufficient protection against reinfection, with studies demonstrating same-type reinfection rates ranging from 0.8 to 108.99 reinfections per 1000 person-years in different populations [18–20]. As the magnitude of humoral responses to HPV is generally log orders lower than the magnitude of responses to vaccination among both women [21] and men [22], use of 9vHPV likely confers greater protection against future infection, regardless of prior exposure.

Burden of Disease Avertible by Midadult HPV Vaccination

While HPV vaccination in midadulthood is safe and effective and unvaccinated midadults may be susceptible to infection with ≥1 9vHPV type, estimates of the burden of disease preventable by vaccination in midadulthood are necessary to assess the public health utility of any policy recommendation. Mathematical or computational models are commonly used to estimate the expected impact of an intervention on disease burden and disease-associated costs. In formulating their recommendation for midadult HPV vaccination, the ACIP reviewed findings from 5 models estimating averted disease and the cost-effectiveness of this strategy [23–26], developed by academic research (HPV-Advise [23], Cancer Intervention and Surveillance Modeling Network [CISNET] [26]), government (Chesson et al. [24], HPV-Advise), and industry groups (Daniels et al. [25]). The outcomes for all models included anogenital warts, CIN, and cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancers (Supplementary Table 1). Two models (Chesson et al. [24] and Daniels et al. [25]) additionally modeled RRP. Daniels et al. also included vaginal intraepithelial neoplasia [25]. All models included HPV 16/18/31/33/45/52/58. All models except the CISNET models [26] also included HPV 6/11, the main etiologies of anogenital warts. Chesson et al. did not directly model transmission in their simplified modeling framework (Supplementary Table 2) [24], and all other models considered transmission only within heterosexual partnerships. Four of the 5 models assumed 95% vaccine effectiveness against infection with targeted HPV types, while Daniels et al. [25] allowed for differing levels of protection against transient (41%–96%) vs persistent infection (>96%), as well as differences in protection across HPV types and anatomical sites (Supplementary Table 3).

These models estimated total effects of expanding HPV vaccinations to all midadults, compared with vaccination among females ≤26 years and males ≤21 years, of 2900–24 500 cervical cancer cases averted over 100 years (Table 1). Models accounting for additional forms of HPV-associated cancers estimated total cancer cases averted to be 20 900–37 900 [24, 25]. Notably, oropharyngeal cancer accounted for the largest proportion of averted cancers (among models with estimates by anatomical site). These findings align with evidence that HPV-associated oropharyngeal cancer incidence now exceeds that of cervical cancer [27]. The median age at oropharyngeal cancer diagnosis is 63 years in women and 61 years in men [28]. Given the lag between HPV acquisition and detectable cancer, this timing likely further supports oral HPV infection during and after midadulthood. A nationally representative study found that oral HPV infection prevalence in 2009–2010 peaked among individuals aged 30–34 and 60–64 [29], highlighting an opportunity for midadult vaccination, which has been associated with considerable reductions in oral HPV infection prevalence [30].

When reconciling findings across these modeling studies, differences in the explicit scenarios modeled merit consideration alongside potential differences in clinical, biological, and epidemiologic assumptions. For instance, whereas the model by Daniels et al. estimated higher numbers of cervical and noncervical cancer cases averted than the other 4 models, these estimates corresponded to scenarios with higher annual uptake of vaccination among midadult females (3.5%) and males (2.8%) than the other 4 models (2.6% and 1.9% uptake among females and males, respectively)

Table 1. Base Case Estimates of Averted Disease and Cost-effectiveness of HPV Midadult Vaccination Models Comparing Universal HPV Vaccination up to 45 Years With Vaccination for Females ≤26 Years and Males ≤21 Years

Measure	HPV-ADVISE [21]	Chesson et al. [22]	Daniels et al. [23]	CISNET –Harvard [24]	CISNET –Policy1-Cervix [24]
Additional cancer cases averted	6500[a]	20 934	37 856	NP	NP
Cervical	2900[b]	5141	15 721	13 200	24 500
Noncervical[c] total	3600[b]	15 793	22 135	NP	NP
Oropharyngeal	NP	8593	11 131	NP	NP
Additional anogenital warts cases averted	123 700[b]	102 691	1 743 461	NP	NP
Additional RRP cases averted	NA	421	8688	NA	NA
Additional cost per QALY gained in USD	$1 471 000[b]	$653 300	$141 000	$440 600	$315 700

Abbreviations: NA, not applicable, indicates not included as an outcome; NP, not presented, indicates included in model but not presented in published material; QALY, quality-adjusted life-year; RRP, recurrent respiratory papillomatosis.

[a]Sum of reported estimates for cervical and noncervical cancers; not estimated in original study.

[b]Median estimate of 50 best-fitting parameter sets.

[c]Noncervical cancers include oropharyngeal, anal, penile, vaginal, and vulvar cancers.

(Supplementary Table 3) [23–26]. However, the magnitude of differences in estimates of anogenital warts cases averted (1 743 461 for Daniels et al. vs 102 691–123 700 for other models) and RRP cases averted (8688 for Daniels et al. vs 421 for Chesson et al.) cannot be explained by this factor alone [24, 25]. Variations in baseline disease incidence, probabilities of progression from HPV infection to HPV-associated disease, and HPV-attributable fractions of disease likely additionally contribute to differences in findings between the models (Supplementary Table 4).

The models further estimated that midadult vaccination would prevent 102 700–1 743 500 cases of anogenital warts [23–25]. Prevention of anogenital warts may be of particular relevance to high-risk groups for whom the ACIP has not issued specific guidance around midadult HPV vaccination. For instance, while the prevalence of anogenital warts was estimated at approximately 2–3 cases per 1000 persons aged 18–39 years within large commercially insured cohorts within the United States [31], a >10-fold higher prevalence has been estimated among populations served by sexual health clinics [32]. Although the morbidity of anogenital warts is low compared with that of HPV-associated cancers, the condition can have profound implications for patients' self-reported quality of life [33, 34]. Wide variation in estimates of averted anogenital warts cases preventable by midadult vaccination across the modeling studies highlights uncertainties in the relationship between vaccination and anogenital warts prevention.

Only 2 of the models included RRP in their estimates (Chesson et al. and Daniels et al.), estimating that midadult vaccination could prevent 421–8 688 cases of RRP over 100 years [24, 25]. Although rare (estimated at 4 cases per 100 000 children and 2 cases per 100 000 adults), RRP can cause serious morbidity as related breathing obstructions may require frequent surgical intervention [35]. Mothers with HPV can infect children during birth. Thus, HPV vaccination may be an important prepregnancy consideration for some individuals.

Results of modeling studies must be interpreted in the context of our knowledge of underlying processes that investigators aim to simulate. All models were limited in their ability to adequately represent the heterogeneity of sexual partnership formation and, thus, impacts of vaccination on individuals' risk of acquiring and transmitting HPV. Whereas all models explicitly addressing sexual partnership formation accounted for assortative mixing across age groups and risk strata, the difficulty of measuring these sexual network properties in the real world hinders assessments of external validity [36, 37]. Further behavioral considerations, such as differences in vaccine uptake and screening behavior among individuals with differing risk behaviors, may additionally limit the real-world applicability of modeling estimates that assume relatively uniform health care–seeking. Only 83% of eligible women underwent cervical cancer screening, an important secondary prevention mechanism, in compliance with existing guidelines as of 2018 [38]. Sensitivity analyses in the CISNET midadult vaccination models found that imperfect screening resulted in greater impact and cost-effectiveness of midadult vaccination [26]. As described above, uncertainties also surround the prevalence, strength, and duration of naturally acquired immunity against homologous HPV type reinfection. These factors are important to estimate the proportion of the midadult population that may benefit from 9vHPV vaccination. While all midadult vaccination models considered that <100% of HPV infections would result in protective, type-specific immunity against reinfection, each model treated naturally acquired immunity differently, with some assuming waning and others lifelong protection (Supplementary Table 3). Finally, uncertainty about the latent period between HPV acquisition and subsequent cancer remains. For cervical cancer, a study using multiple models estimated the median time from infection to detectable cancer at 17.5 to 26.0 years [39]. As there is no regular screening for precancerous lesions at noncervical sites, the latent period in noncervical HPV-associated cancers is less firmly established.

In the modeling studies discussed here, 3 of the models assumed a vaccine-favorable lag time of 5 years between vaccination implementation and observed reductions in these outcomes [24, 26].

In light of this uncertainty, the need to calibrate multiple parameters of the HPV clinical course within each modeling study suggests that each study may have limitations. Added biological and epidemiologic complexity may offer limited value when the underlying disease and transmission processes are inadequately understood [40]. Regardless of inconsistencies in frameworks and specific predictions, the results of the modeling studies are aligned in indicating that a substantial number of HPV-associated disease cases can be prevented by midadult vaccination, given the persistent challenges of delivering HPV vaccines to all eligible US children, adolescents, and young adults. This body of evidence in support of the public health impact of midadult HPV vaccination complements RCTs that have demonstrated safety, immunogenicity, and clinical efficacy.

Cost-effectiveness Considerations for Midadult HPV Vaccination

Public health decision-makers must additionally account for considerations of reasonable and efficient resource allocation. Cost-effectiveness analyses, which weigh the costs of implementing an intervention against the burden of disease averted and costs from treatment or death and disability, provide additional metrics to inform population-level implementation of interventions. The modeling studies described above included assessments of the cost-effectiveness of HPV midadult vaccination, estimating the costs incurred per quality-adjusted life-year (QALY) gained. Each modeling study derived cost estimates from previously published studies of real-world health economic data, adjusted to 2018 (USD) prices, and incorporated disutility due to morbidity associated with these conditions into cost-effectiveness estimates [23–26].

Under the base-case scenarios considered in these studies, estimated costs of universal midadult vaccination amounted to $141 000–$1 471 000 per QALY gained [23–26]. Direct comparisons of these estimates across studies are inappropriate given differences in the specific disease outcomes each model assessed (Table 1). It is unsurprising, for instance, that the HPV-Advise model, which had the lowest estimate of vaccine-preventable cancer cases (6500, including 2900 due to cervical cancer), estimated 2.3–10.4 times higher costs per QALY gained [23] than the other models, which estimated 5100–24 500 preventable cases of cervical cancer and 13 200–37 900 total preventable cancer cases [24–26]. However, several consistencies and inconsistencies across the studies merit specific consideration. All models assumed similar costs for HPV vaccination and for treatment of cervical cancer and assumed disutility during cancer treatment (Supplementary Table 5) [23–26]. In addition to estimating the greatest burden of both cancer cases and anogenital warts cases avertible by vaccination, the model by Daniels et al. assumed greater quality-of-life detriments associated with CIN and genital warts cases, greater long-term disutility among cancer survivors, and higher costs for treatment of CIN, anogenital warts, and vulvar, vaginal, anal, oropharyngeal, and penile cancers as well as RRP [25]. These factors could contribute to the relatively lower estimates of costs per QALY gained in this study as compared with the others, even if estimates of vaccine-preventable disease burden were similar.

The ACIP does not endorse specific cost-effectiveness thresholds in its decision-making procedures [41]. Whether an intervention meets criteria for being cost-effective at the population level depends upon what stakeholders are willing to pay for the public health benefits. For instance, costs of serotype B meningococcal vaccination, which is recommended by the ACIP for adolescents and young adults aged 16–23 years [42], have been estimated at up to $13.9 million per QALY gained [43]. Although cost-effectiveness at a given willingness-to-pay threshold may be a useful guidepost for informing public health investments, it does not inform decision-making for individual patients who may benefit from immunization.

Factors Relevant to SCDM for Midadult Vaccination Against HPV

The ACIP recommendations note that clinicians can consider discussing HPV vaccination with the persons aged 27–45 years most likely to benefit from immunization [3]. However, lack of guidance on relevant considerations may pose a barrier to deciding which patients may benefit from HPV vaccination. Existing literature and the midadult vaccination models highlight important considerations and uncertainties that can inform SCDM. Because HPV is sexually transmitted, dialogue around sexual behavior is an important component of SCDM to ensure that midadult patients who may benefit from HPV vaccination are aware of the opportunity to receive this intervention. However, providers may face challenges in identifying the midadults most likely to benefit; sexual health may not be discussed in detail, and patients may be unaware of whether they will be at risk of exposure to HPV in the future. Thus, while knowledge of an individual patient's risk factors for HPV infection may help to identify the patients who may benefit from vaccination, absence of known risk factors for a patient should not prevent providers from initiating SCDM conversations around 9vHPV.

Likelihood of Existing HPV Immunity

As previously noted, most unvaccinated midadults lack prior exposure to at least 1 of the 9vHPV types, and evidence for protective immunity from prior natural exposure is lacking. Growth in vaccine coverage among midadults is expected as those vaccinated as adolescents or young adults enter midadulthood. Reassuringly, durable vaccine-associated antibody

responses persist for ≥10 years among women [44] and ≥5 years among men [22]. However, in 2020, full HPV vaccination coverage among 17-year-olds was <65% [45]. Lower vaccination coverage among adolescents and young adults results in lower population-level herd immunity, making midadult vaccination more beneficial both at individual and population levels.

Potential for New HPV Acquisition

Individuals' likelihood of risk for future HPV infection should also inform SCDM. As HPV risks increase with number of sexual partners, individuals anticipating new partnerships in midadulthood and beyond may benefit from vaccination. Condomless sex with nonsteady partners is a risk factor for HPV acquisition among men [46] and women [47]; additionally, individuals reporting that their partners are not monogamous are at increased risk [48]. Consideration may also be given to anticipated partners' likelihood of immunity via vaccination, especially in age-disparate partnerships: A study of heterosexual men in Australia found that the odds of having anogenital warts among men with partners who were in birth cohorts eligible for HPV vaccination were half those of men with partners not eligible for vaccination [49].

Considerations for Men Who Have Sex With Men and Transgender Populations

Not considered in the midadult vaccination models, men who have sex with men (MSM) comprise a high-risk population for HPV infection [50]. MSM account for disproportionate shares of cases of anogenital warts [51, 52] and HPV-related cancers among men [53] and may derive limited indirect benefit from uptake of HPV vaccination among the heterosexual population. While the ACIP recommendations do not include specific considerations for MSM, precedent for targeted vaccination based on sexual risk exists (eg, hepatitis A [54] and B [55] vaccinations).

Enhanced attention to the need for HPV vaccination may also be appropriate for transgender and gender-nonbinary populations. While data are limited, studies have identified high prevalence of HPV infection coupled with limited vaccine uptake and awareness of HPV vaccination among transgender and nonbinary persons [56, 57]. Given the high prevalence of anogenital warts and anal dysplasia among transgender women [56, 58], as well as suboptimal awareness and utilization of anal cancer screening [59, 60], vaccination remains an important strategy within this population.

Patient and Clinician Uptake and Perspectives on HPV Vaccination for Midadults

Few midadults are likely to have received HPV vaccination as adolescents due to their age at the time of initial recommendations. Population-level reports on uptake and coverage of HPV vaccination among midadults are sparse and all from before the SCDM recommendation. National Health Interview Survey (2017) data found that 16% of females and 3% of males age 27–45 years self-reported having received ≥1 dose of HPV vaccine [61]. A small number of studies among midadult subpopulations, including high-risk sexual minority populations, estimated coverage rates ranging from 14% to 37% [62–65].

Few midadults are aware of HPV vaccination eligibility: A 2020 national survey found that only 38% of midadults were aware that HPV vaccination was approved for ages 27–45 years [66]. When told of the new recommendation, 56% of midadults were likely to ask their clinician about HPV vaccine, and 43% were likely to get the vaccine. One study of midadult MSM, conducted in 2015 before the midadult SCDM recommendation, reported that 67% would likely initiate vaccination if recommendations allowed [67]. Several studies have examined reported reasons for not being vaccinated among HPV vaccine–eligible adults [62, 64, 68]. These studies found that the main reason was that vaccination had not been recommended by a doctor (20%–44%), underscoring the need for clinicians to initiate SCDM around HPV vaccination.

Despite the important role of clinicians in vaccination [69, 70], few studies have examined clinician knowledge, attitudes, and behaviors related to midadult HPV vaccination. A study of internal medicine and family physicians conducted shortly after the SCDM recommendation in 2019 found that 58% of respondents were aware of the ACIP recommendation, and 42% had made recommendations to their midadult patients, although many had done this infrequently (22% to ≤3 patients) [71]. Although a majority (54%–88%) reported being more likely to recommend HPV vaccination to at least some patients following the 2019 ACIP recommendation, 57% were not sure what to emphasize in SCDM. A survey of obstetricians and gynecologists found that 94% were aware of the SCDM recommendation and 55% routinely recommended HPV vaccination to midadult patients [72]. A third study found that clinicians were more likely to recommend HPV vaccination to midadult females (26%) compared with males (17%) [73]. As the incidence of HPV-associated diseases, such as oropharyngeal cancer, rises among males, SCDM for midadult vaccination with all patients is important. Primary care clinicians and urologists may thus have important roles in SCDM for male patients. Additionally, clinicians more often cited failure of insurance coverage for vaccination as a barrier for midadult patients (75%) compared with young adults (59%) [72], although HPV vaccination for midadults is covered preventative care under the Affordable Care Act.

CONCLUSIONS

Although HPV vaccination has been widely studied in younger populations, data on midadult vaccination are limited,

presenting challenges for clinicians and midadult patients in making informed decisions related to HPV vaccination. Public health models of midadult vaccination and existing literature highlight key considerations for vaccination in this age group and may inform SCDM discussions. Given challenges in identifying patients who could benefit from HPV, greater awareness of SCDM considerations among clinicians and midadult patients and widespread implementation of SCDM for HPV vaccination may help accelerate progress toward cervical cancer elimination and reduce morbidity and mortality from other HPV-associated diseases.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. This study does not include factors necessitating patient consent. This study does not qualify as human subjects research.

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